

PATENT COOPERATION TREATY

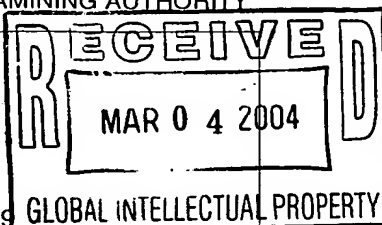
IPM/RHB

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Levy, David J.
GLAXOSMITHKLINE
Corp. Intellectual Prop. Dept.
Five Moore Drive
Research Triangle Park, NC 27709
ETATS-UNIS D'AMERIQUE



NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

20.02.2004

Applicant's or agent's file reference
PU4722WO

IMPORTANT NOTIFICATION

International application No.
PCT/US 03/05723

International filing date (day/month/year)
25.02.2003

Priority date (day/month/year)
28.02.2002

Applicant
SMITHKLINE BEECHAM CORPORATION et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Janzing, M

Tel. +31 70 340-4140



PATENT COOPERATION TREATY

PCT Rec'd PCT/PTO 23 AUG 2004

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)



Applicant's or agent's file reference PU4722WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/US 03/05723	International filing date (day/month/year) 25.02.2003	Priority date (day/month/year) 28.02.2002
International Patent Classification (IPC) or both national classification and IPC C07D277/26		
Applicant SMITHKLINE BEECHAM CORPORATION et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☒ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 11.08.2003	Date of completion of this report 20.02.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Allard, M Telephone No. +31 70 340-2002 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US 03/05723

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-43 as originally filed

Claims, Numbers

1-24 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US 03/05723

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - ☐ the entire international application,
 - ☐ claims Nos.
because:
 - ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☒ the claims, or said claims Nos. 18-23 (all in part) are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
 - ☐ the written form has not been furnished or does not comply with the Standard.
 - ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:
 - ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
 - ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US 03/05723

☒ all parts.

☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-24
	No: Claims	-
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-24
Industrial applicability (IA)	Yes: Claims	1-24
	No: Claims	-

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US03/05723

Reference is made to the following documents:

- D1: WO 01 00603 A (GLAXO GROUP LIMITED) 4 January 2001 (2001-01-04)
- D2: BEBBINGTON D ET AL: '3,5-Disubstituted-4-hydroxyphenyls linked to 3-hydroxy-2-methyl-4(1H)-pyridinone: potent inhibitors of lipid peroxidation and cell toxicity' JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 15, 27 July 2000 (2000-07-27), pages 2779-2782, XP002243103
- D3: SATO R ET AL: 'Efficient synthesis and biological properties of new benzopentathiepins' HETEROCYCLES, vol. 41, no. 5, 1 May 1995 (1995-05-01), pages 893-896, XP002243104
- D4: TERCIO J ET AL: 'Synthesis of 2,2-dimethyl-2H-thiochromenes, the sulfur analogs of precocenes' SYNTHESIS, no. 2, February 1987 (1987-02), pages 149-153, XP002139430
- D5: ENGMAN L ET AL: 'A general procedure for the synthesis of methylthio-, methylseleno- and methyltelluro- substituted aromatic compounds' JOURNAL OF ORGANOMETALLIC CHEMISTRY, vol. 296, no. 3, 3 December 1985 (1985-12-03), pages 357-366, XP002243105
- D6: MALMSTRÖM J ET AL: 'Novel antioxidants: unexpected rearrangements in the radical cyclization approach to 2,3-dihydrobenzo[b]thiophene-5-ol derivatives' JOURNAL OF ORGANIC CHEMISTRY, vol. 63, no. 10, 15 May 1998 (1998-05-15), pages 3318-3323, XP002243106
- D7: GAUTHIER J Y ET AL: 'A remarkably simple conversion of nitriles to thioamides' PHOSPHORUS, SULFUR AND SILICON AND THE RELATED ELEMENTS, vol. 95/96, no. 1/4, 1994, pages 325-326, XP000654912 cited in the application

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

It appears from the description of the application (see page 28) and from the chemistry involved, that the process of claims 18-23 can only lead to thiazole derivatives of formula (III) according to claim 18, wherein Y is S and Z is N. **The preliminary examination of claims 18-23 is therefore limited to the preparation of such compounds (III).**

Re Item IV

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US03/05723

Lack of unity of invention

The present application concerns

- a process for preparing substituted phenylthiomethyl-(thi)(ox)azoles by condensation of (thi)(ox)azole-methanol derivatives, including the corresponding halides, with a thiophenol generated (*in situ*) from the corresponding phenyl halide (claims 1-12, 24), and certain intermediates useful in said process (claims 13-17) on the one hand,
- and a process for preparing thi(ox)azole-methanol derivatives (claims 18-23) on the other hand.

D1 discloses a process for preparing the present substituted phenylthiomethyl-(thi)(ox)azoles by condensation of (thi)(ox)azole methanol derivatives, including the corresponding halides, with a thiophenol generated from phenylsulphonyl chloride (see example 67) or from a phenyl thiocarbamate (see *inter alia* intermediate 25 and examples 63, 65 and 82).

D1 furthermore discloses the preparation of (thi)(ox)azole-methanol derivatives corresponding to the compounds subject-matter of claims 13-17 of the present application, see *inter alia* intermediates 1, 4, 7 and 9.

It appears therefore that the problems underlying the application can be seen in the provision of

- a further process for preparing thiophenols to be used in the preparation of phenylthiomethyl-(thi)(ox)azoles, and of
- a further process for preparing (thi)(ox)azole methanol derivatives.

These problems are solved respectively by

- claims 1-17, 24 (**invention 1**)
- claims 18-23 (**invention 2**)

As said (thi)(ox)azole methanol derivatives are however known from D1, and cannot constitute a special technical feature, and as moreover the claimed processes have no further technical features in common, it results that the application does not fulfill the

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US03/05723

conditions of Rule 13.2 PCT and lacks unity of invention within the meaning of Rule 13.1 PCT.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Article 33(2) PCT)

- Invention 1:

The available prior art does not disclose the processes and compounds of claims 1-17 and 24, whose subject-matter is therefore novel.

- Invention 2:

The available prior art does not disclose the process of claims 18-23, whose subject-matter is therefore novel.

Inventive step (Article 33(3) PCT)

- Invention 1:

D1, which is considered to represent the closest prior art, describes a process for preparing compounds (IV) of the present application by reacting a thiophenol A with a compound C (see D1, page 14) corresponding to compounds III of the present application, see D1, examples 63, 65, 67 and 82. The thiophenol A is prepared in D1 from the corresponding dimethylcarbamoylthio derivative, see D1, page 36 and 37, procedure 5, and page 24, intermediate 25.

In the light of the teachings of D1, a first problem underlying and solved by the present application can be seen in a further process for preparing compounds (IV).

To solve this problem, the present application proposes to replace in the process disclosed in D1 the step of preparation of the thiophenol A according to D1 by a step of

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US03/05723

metallation of a halophenyl derivative (I) according to the present application, followed by treatment with sulfur.

Such a process for preparing thiophenols is however well known in the art, see D3, page 894, scheme 1, step 2 to 3; D4, page 152, scheme, step 9 to 2g; and D5, the whole document.

The transposition of the process of D3-D5 to solve the given problem is therefore an obvious measure, which does not involve an inventive step.

The intermediates of claims 13 and 16 cannot bring a positive contribution to an inventive step, because protection of a phenolic group by its silylether during similar reactions is already known from D2 (see page 2780, scheme 1, step xvi) and D6 (see page 3319, scheme 1).

The subject-matter of claims 1-17 and 24 lacks therefore an inventive step.

- Invention 2

D1, which is considered to represent the closest prior art, describes a process for preparing thiazole derivatives (III) of the present application by cyclisation of a substituted thiobenzamide, see D1, intermediates 10, 12 and 33-39, and page 26, general procedure B. The substituted thiobenzamide is prepared by treatment of the corresponding benzamides with P_4S_{10} , see D1, general procedure A and intermediates 26-32.

In the light of the teachings of D1, a second problem underlying and solved by the present application can be seen in the preparation of further thiazoles (III).

To solve this problem, the present application proposes to prepare the thiobenzamides for cyclisation to the thiazoles by treatment of the corresponding nitrile (XVII) with thioacetic acid.

Such a process is however already disclosed in D7, and its transposition to solve the given problem does not involve an inventive step.

The subject-matter of claims 18-23 lacks therefore an inventive step.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US03/05723

Industrial applicability (Article 33(4) PCT)

The compounds and processes of claims 1-17 and 24 (**Invention 1**) and of claims 18-23 (**Invention 2**) can be applied in the chemical industry.

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